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# News about the genetics of congenital primary adrenal insufficiency

## *Nouveautés sur la génétique des insuffisances surrénales primaires*

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**Abstract**

Primary adrenal insufficiency (PAI) is characterized by impaired production of steroid hormones due to an adrenal cortex defect. This condition incurs a risk of acute insufficiency which may be life-threatening. Today, 80% of pediatric forms of PAI have a genetic origin but 5% have no clear genetic support. Recently discovered mutations in genes relating to oxidative stress have opened the way to research on genes unrelated to the adrenal gland. Identification of causal mutations in a gene responsible for PAI allows genetic counseling, guidance of follow-up and prevention of complications. This is particularly true for stress oxidative anomalies, as extra-adrenal manifestations may occur due to the sensitivity to oxidative stress of other organs such as the heart, thyroid, liver, kidney and pancreas.


*Keywords:* Primary adrenal insufficiency; Genetics; Steroid biosynthesis; Adrenal development; Massively parallel sequencing

**Résumé**

L'insuffisance surrénale primaire (ISP) se caractérise par un déficit en hormones stéroïdiennes lié à un trouble du cortex surrénal qui expose au risque d'insuffisance aiguë et de menace vitale. Actuellement, 80 % des formes pédiatriques d'ISP sont d'origine génétique et 5 % restent sans étiologie génétique identifiée. Les récentes découvertes de mutations de gènes du stress oxydant ouvrent le champ des recherches d'anomalies génétiques non spécifiques de la glande surrénale. L'identification du gène responsable d'une ISP permet un conseil génétique, d'orienter le suivi à long terme et de prévenir d'éventuelles complications, en particulier dans celles dues à des anomalies du stress oxydant où d'autres organes sensibles au stress oxydant comme le cœur, la thyroïde, le foie, le rein, le pancréas peuvent être touchés.


*Mots clés :* Insuffisance surrénale primaire ; Génétique ; Stéroïdogenèse ; Développement de la surrénale ; Séquençage parallèle massif

## 1. Introduction

Primary adrenal insufficiency (PAI) is a rare life-threatening disease, with failure of steroid (mineralocorticoid and/or glucocorticoid) hormone production due to an adrenal cortex defect. Unlike PAI, secondary AI is caused by central defects with ACTH insufficiency and will not be detailed in this review. Consequent to disruption of adrenal mineralocorticoid or glucocorticoid production, the renin angiotensin aldosterone loop and hypothalamus pituitary axis are respectively stimulated, resulting in increased renin and/or ACTH synthesis.

In adult patients, 80% of PAIs are of autoimmune origin, whereas in children they are mostly (80%) due to genetic defects [1,2]. Depending on the cohort studied, proportions may vary but 55–75% of PAIs in children consist in congenital adrenal hyperplasia (CAH). About half of the other 35–45% of cases

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are of autoimmune origin, and the other half are mostly due to genetic defects other than CAH. Proportions may also vary according to patient age. Genetic PAI occurs most often during the first months of life, and more rarely during infancy. Clinical signs may be non-specific in children, with fatigue, nausea and vomiting or abdominal pain, or may be more specific with signs related to hypoglycemia due to glucocorticoid deficiency, such as seizures, or to mineralocorticoid deficiency with salt-wasting and dehydration. Most cases concern congenital CAH [1,2], which in France is easily diagnosed on neonatal screening (with elevated 17OH-progesterone) and confirmed by genetic analysis. 21-hydroxylase deficiency accounts for 95% cases of CAH, with a few cases implicating *HSD3B2* defects [3]. Both are involved in steroid biosynthesis. Genetic mutations in other genes encoding proteins involved in steroid biosynthesis and signaling or in adrenal development account for another 10% of cases. In older children, an autoimmune origin accounts for 10–15% of cases and is the first etiology to be screened for. It can be part of an APECED syndrome due to *AIRE* gene defects. The second most frequent cause, in boys, is adrenoleukodystrophy, due to *ABCD1* gene defects [1,2]. Five percent of genetic PAIs in children remain without any genetic diagnosis.

There are 3 types of PAI: isolated mineralocorticoid or glucocorticoid deficiency, or combined mineralocorticoid-glucocorticoid deficiency (global adrenal insufficiency). Many genes are involved in each type, and a given gene may be responsible for different types. Thus, every associated clinical signs must be reported in order to refine the molecular strategy and the order of gene analysis. The spectrum of genetic causes has increased with the development of massively parallel sequencing (MPS). MPS is now able to perform millions of sequences and simultaneously study several genes in several patients, accelerating diagnosis. Above all, MPS is the leading technique for new gene discoveries, which have recently found involvement of genes not specifically related to the adrenal gland, but notably involved in oxidative stress defense (*NNT, TXNRD2*, etc.) or in growth in certain syndromes (*SAMD9, CDKN1C*, etc.).

This review focuses on the genetic causes of PAI, except for HCS (CYP21A2, HSD3B2), adrenoleukodystrophy and autoimmune origins, and presents the recent advances. Table 1 summarizes the most frequent etiologies of inherited PAI in children (excluding some rare syndromes).

## 2. PAI with isolated mineralocorticoid deficiency

PAI with isolated mineralocorticoid deficiency is also called aldosterone synthase deficiency. This defect reveals mostly in the neonatal period by salt-wasting associated with vomiting or delayed growth. Clinical symptoms are always severe in the neonatal period and improve with age. Diagnosis is founded on hormonal data, with hyperreninemic hypoaldosteronism but normal levels of ACTH and cortisol. It should be borne ion mind that there is a transient neonatal physiological resistance to aldosterone, explaining aldosterone levels of around 1800 pmol/L in the first month of life, decreasing to a mean 500 pmol/L from 3 months [4]. In almost all cases, this defect is due to autosomal recessive mutations in the *CYP11B2* gene encoding aldosynthase, the specific enzyme of the zona glomerulosa (Fig. 1). When genetic analysis of *CYP11B2* is negative, the *DAX-1* gene should be tested in boys (X-linked transmission). Initial presentation of combined mineralocorticoid-glucocorticoid deficiency may simulate isolated mineralocorticoid deficiency, although careful biological exploration shows ACTH elevation, preceding clinical cortisol deficiency. Nevertheless, an atypical case with a moderate *DAX-1* mutation was reported as having only isolated mineralocorticoid deficiency [5].

## 3. PAI with combined mineralocorticoid-glucocorticoid deficiency

In PAI with combined mineralocorticoid-glucocorticoid deficiency, also known as global adrenal insufficiency, molecular orientation differs according to sex.

### 3.1. Global AI due to adrenal development defect

The most frequent disorder in boys (X-linked recessive disorders) in the neonatal period is due to *DAX-1* (*NR0B1*) mutations [6]; the other frequent X-linked recessive disorder is adrenoleukodystrophy, with onset usually after 3 years of age. Dosage-sensitive sex reversal adrenal hypoplasia congenita critical region on the X-chromosome, gene 1 (DAX-1) is a nuclear receptor involved in adrenal development. Hypoplasia in this case is histologically characterized by the presence in the adrenal glands of large vacuolated cells reminiscent of those of the fetal zone of the adrenal gland, and thus called X-linked cytomegalic form. It may be part of a contiguous gene syndrome together with the Duchenne muscular dystrophy gene (*DMD*) and glycerol kinase deficiency gene (*GKD*). Diagnosis may be made later, at an age of 14–20 years, based on adrenal insufficiency accompanied by delayed puberty. This adrenal insufficiency is associated with hypogonadotropic hypogonadism (HHG) and infertility that occurs in all boys with puberty [7].

Today only one other gene involved in adrenal development, *SF1* (*NR5A1*), has been implicated in adrenal insufficiency (4 cases) [8], but associated with disorders of sexual development (DSD). In 2004, our team and Mendonca's group found mutations in a heterozygous state for *SF1* gene in patients with isolated gonadal dysgenesis without adrenal insufficiency [9]. Since then many mutations (> 100) have been reported in isolated gonadal dysgenesis [10].

Other genes (*CITED2*, *PBX1*, etc.) are candidates for PAI based on findings in animals but pathogenic mutations have not yet been found in human [11–13].

### 3.2. Global AI due to steroid biosynthesis defect

PAI with combined mineralocorticoid-glucocorticoid deficiency could result from a defect in steroid biosynthesis. Its isolated form without DSD is observed in either 46,XY patients with 21-hydroxylase deficiency or 46,XX patients with HSD3B2, StAR or CYP11A1 mutations (Fig. 1). In a newborn female phenotype with severe salt loss, an abnormality

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